IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Lorraine Elisabeth Pena and
Maw-Sheng Wu

Confirmation No.: 5718

Application No.: 09/634,399

Group Art Unit: 1617

Filing Date: August 9, 2000

Examiner: Lauren Q. Wells

For: NOVEL COMPOSITIONS OF MINOXIDIL

Assistant Commissioner for Patents
Washington DC 20231

Sir:

DECLARATION OF LORRAINE E. PENA UNDER 37 C.F.R. § 1.132

I, Lorraine E. Pena, Ph.D., hereby declare the following:

(1) I received my Bachelor of Science Degree in Chemistry and German from the University of Missouri-Kansas City in 1975. I received my Ph.D. degree in Pharmacy from the same university in 1980.

(2) I have extensive experience in the field of pharmaceutical formulation chemistry and have been extensively involved during the past 24 years in the development of pharmaceutical compositions for topical applications. In particular, I have had extensive experience in the preparation of pharmaceutical compositions containing minoxidil for topical applications.

(3) I am employed as an Associate Research Fellow at what has recently become known as Pfizer Inc. (previously Pharmacia Corporation, to whom the present application was originally assigned). As set forth in my *curriculum vitae*, a copy of which is attached hereto as

Exhibit 1, I have been associated with Pharmacia Corporation or its predecessors in interest, since 1980. My further experience and qualifications, including my patents and publications, are also set forth in my *curriculum vitae*.

(4) I am a joint inventor of the subject matter claimed in the above-identified application, and have studied and am familiar with the Examiner's Office Action dated July 14, 2004, and the references cited therein, including, in particular, Preuilh et al., U.S. Patent No. 6,106,848 (hereinafter "Preuilh"), Ewers,et al, WO 97/03709 (translation, hereinafter "Ewers"), and Pena, U.S. Patent No. 5,225,189 (hereinafter "Pena"). With regard to the Pena patent, I am the sole inventor of the subject matter claimed therein.

(5) Independent Claim 1 in the present application defines single-phase gel compositions comprising from greater than 3% to about 8% minoxidil, a thickening agent, and a pharmaceutically acceptable solvent, in which the minoxidil is completely solubilized in the composition. The thickening agent in Claim 1 is defined as being a non-carbomeric organic agent other than hydroxypropyl cellulose.

Independent Claim 36 defines single-phase gels that contain greater than 3% minoxidil, greater than 50% of a pharmaceutically acceptable solvent, and up to 25% water. The compositions defined by this claim are thickened with a solvent-tolerant carbomer, such as, for example, Carbopol® Ultrez™ 10. As with the compositions defined in Claim 1, the minoxidil is completely solubilized in the claimed compositions.

Independent Claim 62 defines single-phase gel compositions containing greater than about 3% to about 8% minoxidil, together with specified amounts of a polyol, an alcohol, a non-carbomeric polymer (other than hydroxypropyl cellulose), and a sufficient quantity of water. A neutralizing agent may also be present, in concentrations of up to 3%. As with the compositions

defined in the other independent claims, Claim 62 recites that the minoxidil is completely solubilized in the claimed compositions.

(6) The Office Action dated July 4, 2004 alleges that the pending claims are obvious, and therefore unpatentable. The teachings of Preuilh, together with Ewers and Pena, are combined to reject many of the claims. Additional references, including Samour, U.S. Patent No. 5,620,980, Sine et al., U.S. Patent No. 6,423,329, Anton et al., U.S. Patent No. 5,798,426 and Grollier, GB 2194887, are additionally cited in rejections directed to the remaining claims. All of the rejections are derived from that based on Preuilh, in view of Ewers and Pena, however.

(7) Preuilh is directed to oil-in-water emulsions that contain, in addition to the oil (fatty phase) and water (aqueous phase), 30% to 50% of a pro-penetrating glycol, an emulsifying agent and a biologically active agent. A laundry-list of biologically active agents, including minoxidil, is provided, and Preuilh indicates that the compositions can comprise from 0.0001% to 20% by weight of the active agent. Preuilh further teaches that a polymeric emulsifier, such as Pemulen TR1, Pemulen TR2, Carbopol 1342 or Carbopol 1382, may be used as the emulsifying agent to stabilize the disclosed emulsions. Preuilh also states that a gelling or thickening agent, such as hydroxypropylcellulose, or a carbomer, such as Carbopol 910 or 934, can further be included to thicken the emulsion. A single example of an exemplary emulsion is set forth in Preuilh in Example 1. However, no information is provided regarding the manner in which the emulsion was formulated such as, for example, processing steps, processing conditions, order of addition, and the like.

(8) Preuilh clearly does not teach or suggest the compositions claimed in the present application. In this regard, the present claims distinguish fundamentally over the Preuilh patent

in that Preuilh is directed solely to the preparation of biphasic emulsions in which an oil (or fatty) phase is dispersed in a water (or aqueous) phase. In contrast, the presently claimed compositions are single-phase gels, *i.e.*, semisolids which comprise organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid.

(9) The present claims further define over the Preuilh patent in that Preuilh fails to disclose or suggest the use as thickening agents of non-carbomeric materials, such as acrylate/C_{10-30} alkyl acrylate crosspolymers, or solvent-tolerant carbomers, such as Carbopol® Ultrez™ 10. Moreover, although Preuilh includes minoxidil in a laundry list of suitable biologically active agents, no examples of any minoxidil-containing compositions are provided. Preuilh also indicates that the compositions can comprise from 0.0001% to 20% by weight of the active agent, but the reference is silent as to the degree of solubilization of the active agent in the disclosed compositions. Thus, although Preuilh may suggest that minoxidil may be included in a very broad range of concentrations, it does not indicate whether the minoxidil would be completely solubilized in either phase of the emulsion. Indeed, it is my opinion, based on my years of working with pharmaceutical formulations of minoxidil, that compositions described in Preuilh, particularly those containing higher concentrations of active agent, if prepared using minoxidil, would not produce stable, pharmaceutically elegant compositions, including compositions in which the minoxidil is completely solubilized.

(10) The Office Action combines Preuilh with Ewers and Pena, stating that it would have been obvious to one of ordinary skill in the art to prepare the minoxidil emulsions described by Preuilh as single phase gels, because Pena describes single-phase minoxidil gel formulations,

and Ewers teaches that gelled emulsions and single-phase gels are interchangeable forms for transdermal applications.

(11) I respectfully disagree with assertions in the Office Action regarding the conclusions that one of ordinary skill in the art would draw from these references, as summarized above. First, since Ewers is directed solely to compositions for topical delivery of the hormone 3-ketodesogestrel, there is no reason that one of ordinary skill in the art, in connection with the preparation of compositions for delivery of a hair-restorative agent like minoxidil, would ever consult, or be likely to encounter Ewers. Moreover, Ewers is focused on the problem of the poor transdermal delivery of 3-ketodesogestrel, and seeks to solve this problem by chemically modifying 3-ketodesogestrel by esterification, which according to Ewers increases transdermal delivery of the hormone. Reference to various delivery forms in Ewers is merely secondary, and is only relevant to the disclosed chemically modified active agent. There is nothing in Ewers that would lead one skilled in the art to view as interchangeable single-phase gels and gelled emulsions generally, let alone single-phase gels and gelled emulsions of minoxidil, as asserted in the Office Action. Indeed, given the aesthetic considerations that would be of major concern with a hair restorative preparation, it is unlikely that one of ordinary skill in the art would ever consider these two delivery forms to be interchangeable. Rather than reach such a conclusion, one of ordinary skill in the art, upon reading Ewers, would likely conclude that chemically modifying a biologically active agent to include an ester group may be useful for increasing that agent's transdermal absorption. Thus, the combination of Ewers with Preuilh may, at best, motivate an ordinarily skilled artisan to prepare Preuilh's emulsions in which the involved active agent is esterified.

(12) Additionally, while Pena describes single-phase minoxidil gels, Pena does not describe gels that contain a non-carbomeric thickening agent or a solvent-tolerant carbomer. Pena contains examples of gels containing up to 3% minoxidil that are thickened with the carbomer Carbopol®934P. As discussed in the specification of the present application, Carbopol®934P is not a solvent-tolerant carbomer. Indeed, Example IV of the present application describes a failed effort to prepare a 5% minoxidil gel using Carbopol®934P. Thus, although Pena suggests that single-phase minoxidil gels may be prepared using the carbomer Carbopol®934P, it does not teach how to make such gels containing higher concentrations of minoxidil, nor does it suggest the use of either solvent-tolerant carbomers or non-carbomeric thickening agents to produce such compositions.

(13) As stated above, based upon my experience and skill in the art of preparing formulations for topical applications, and more particularly in view of my experience working with minoxidil, it is my opinion that the example provided in Preuilh, if prepared with minoxidil as the active ingredient, would fail to produce a stable, pharmaceutically elegant minoxidil composition, particularly if prepared with about 3% or greater minoxidil. To confirm this opinion, I was involved in the preparation and evaluation for stability and pharmaceutical elegance of a minoxidil composition prepared according to the teachings in the Preuilh patent. As a result of this work, I have found that, in contrast to the present invention, stable, pharmaceutically elegant compositions of minoxidil cannot be prepared based on the teachings of Preuilh.

(14) As noted above, Preuilh provides no guidance as to how the disclosed formulations were prepared. Accordingly, I relied upon my skill in the art as a formulator of

topical compositions to select what appeared to me to be appropriate methodology. The components of the composition and their concentrations are as follows:

Cream formulation containing 3% minoxidil according to Example 1 of Preuilh et.al, U.S. Patent No. 6,106,848

Formula for 500 g lot size

	Material	%(w/w)	Amount (grams)
Part I			
	Mineral Oil	20.00	100.00
	Pemulen TR-2	0.30	1.50
Part II			
	Propylene Glycol	47.50	237.50
	Minoxidil	3.00	15.00
	Hydroxypropylmethylcellulose	0.10	0.50
	PEG-6 isostearate	2.00	10.00
	Water	23.00	115.00
Part III			
	Sodium Hydroxide (10% solution)	QS pH 6	
	Water	QS 100%	

The procedure for formulating the above composition is set forth in the attached Exhibit.

(15) After completion of the manufacture, the resulting cream appeared thin but smooth and uniform. However, upon standing overnight, the cream had separated into two phases. In addition, it should be noted that, upon addition of the PEG-6 isostearate to the aqueous phase in Part II, the mixture became cloudy and did not clarify with continued mixing. Due to this cloudiness, it was not possible to determine if the minoxidil was completely solubilized.

(16) On the basis of this experiment, I conclude that Preuilh does not describe a stable, pharmaceutically elegant 3% minoxidil emulsion gel.

(17) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: October 11, 2004

Lorraine E. Pena

Lorraine E. Pena, Ph.D.

EXHIBIT – FORMULATION PROCEDURE

The following is the procedure employed to prepare Preuilh's minoxidil composition.

Part I -- Oil Phase

1. Add mineral oil to a suitably sized vessel and disperse Pemulen TR-2.
2. Mix until uniform.

Part II -- Aqueous Phase

3. In a separate suitably sized vessel, combine the following Part II ingredients: Propylene glycol, water, and PEG-6 isostearate. Mix until uniform.
4. Add the minoxidil to the Part II aqueous phase from step 3 and mix until dissolved.
5. Disperse the hydroxypropylmethylcellulose into the aqueous phase and mix until dissolved and uniform.
6. Add the Part I oil phase from step 2 to the Part II aqueous phase from step 5 with rapid agitation. Mix for a suitable period of time; e.g. 15-20 minutes.

Part III – pH Adjust and QS with H_2O

7. Check pH and adjust to pH 6 with sodium hydroxide 10% solution if necessary.
8. Add sufficient water to a final weight of 500 g and mix until uniform.

Processing notes:

(a) All processing steps were performed at room temperature which is a preferred temperature as is known to those skilled in the art of emulsification with Pemulen TR polymers.

(b) The pH of the cream at step 7 was pH 7.13, so no additional pH adjustment was necessary. In addition, as known to those ordinarily skilled in the art of emulsification with Pemulen TR polymers, addition of an acid to lower the pH to pH 6 (as per the pH of Example 1 of Preuilh) would have been detrimental to the stability of the formulation.

Curriculum Vitae
September 2004

Lorraine Elisabeth Pena, Ph.D.
Associate Research Fellow
Pharmaceutical Sciences-Liquids & Semisolids

Education:

Ph.D., Pharmaceutics, University of Missouri-Kansas City, School of Pharmacy, Kansas City, Missouri, 1980
Major: Physical Pharmacy, Minor: Physical Chemistry
Thesis Title: Rheology and Solution Structure of Gum-Surfactant and Micelle Systems.

B.S., Chemistry & German, University of Missouri-Kansas City, Kansas City, Missouri, 1975.

Employment Experience:

2003-present	Associate Research Fellow, Pharmaceutical Sciences-Liquids & Semisolids, Pfizer Inc., Kalamazoo, Michigan
2001-2003	Research Advisor, Pharmaceutical Sciences-Liquids & Semisolids, Pharmacia Corporation, Kalamazoo, Michigan
1999-2001	Senior Research Scientist, Pharmaceutical Sciences-Liquids & Topicals, Pharmacia Corporation, Kalamazoo, Michigan
1998-1999	Senior Research Scientist, Pharmaceutical Development II-Pharmaceutical Product Development I, Pharmacia & Upjohn, Inc., Kalamazoo, Michigan
1996-1998	Senior Research Scientist, Pharmaceutical Development II-Consumer Products Development, Pharmacia & Upjohn, Inc., Kalamazoo, Michigan
1988-1996	Senior Research Scientist, Drug Delivery R&D-Specialty Products, The Upjohn Company, Kalamazoo, Michigan
1980-1988	Research Scientist, Pharmaceutical Manufacturing Technical Support, The Upjohn Company, Kalamazoo, Michigan
1978-1980	Graduate Teaching Assistant/Tutor, University of Missouri-Kansas City, School of Pharmacy, Kansas City, Missouri
1977-1978	Cosmetic Chemist, C.J. Patterson Company, Kansas City, Missouri

Honors:
Upjohn Laboratories Special Recognition Award-Cyoctol Licensure 1990
TUC Bucks-Cortaid Cream Reformulation Project 1995
TUC Bucks-Preferred Materials PIT 1995
Pharmaceutical Development Special Recognition Award-Cleocin Ovule 2000
Global Supply Special Recognition Award-Cleocin Ovule 2000
Preclinical Patent Award 2002

Professional Affiliations:
American Academy of Pharmaceutical Scientists
Society of Cosmetic Chemists

Products Developed:
Rogaine Solution 2% and 5% with Fragrance
Kaopectate Bismuth Subsalicylate Formulations
Cleocin Vaginal Ovule
Cortaid Cream 1% Maximum Strength
Cleocin/Dalacin T Gel
Regaine Gel 2%
Progaine Shampoo
Topical Medrol 0.25% and 1.0%

US Patents and US and International Published Applications:

LE Pena and DL Huczek, Stable Pharmaceutical Composition Useful for Treating Gastrointestinal Disorders, US2003215524, Published November 20, 2003 , counterpart international application W03/066022 A2, Published August 14, 2003.

LE Pena, PB Bowman, RS Chao, CV Pesheck and CW Jacobsen, Composition and Method for Rectal Delivery of a Lincosamide Antibacterial Drug, US20020197320 A1, Published December 26, 2002.

LE Pena, PB Bowman, RS Chao, CV Pesheck, Intravaginal Clindamycin Ovule Composition, US 6,495,157, issued December 17, 2002; counterpart international application published as WO 01/10407 on February 15, 2001.

LE Pena, VE McCurdy and CS Clark, Composition for Rectal Delivery of an Oxazolidinone Antibacterial Drug, US2003072066, Published September 19, 2002, counterpart international application WO 02/072066 A1, Published September 19, 2002.

LE Pena and MS Wu, Novel Compositions of Minoxidil, International application WO 02/11698 A1, Published February 14, 2002.

LE Pena, Topical Pharmaceutical Compositions. International application WO 94/07478, Published April 14, 1994.

LE Pena and JL Peters, Self-Preserving Conditioning Shampoo Formulation. US 4,938,953, Issued July 3, 1990.

SM Peck, SC Valvani, LE Pena and CJ Thoennes, Foams for Delivery of Minoxidil. International application WO 88/01863, Published March 24, 1998.

DA Hatzenbuhler, JE Browne and LE Pena, Sebum-Dissolving Nonaqueous Minoxidil Formulation. International application WO 88/01502, March 10, 1998.

LE Pena, Minoxidil Gel. US 5,225,189, Issued July 6, 1993, EP 417075 B1, Issued June 9, 1993, counterpart international application WO 89/07436, Published August 24, 1989.

Publications:

LE Pena, PL Possert, JF Stearns, BL Lee and MJ Hageman, "Rheological Characterization of rbSt Oil Suspensions", International Journal of Pharmaceutics, **113**, 89-96, 1995.

LE Pena, BL Lee and JF Stearns, "Structural Rheology of a Model Ointment", Pharmaceutical Research, **11**, 875-881, 1994.

LE Pena, BL Lee and JF Stearns, "Secondary Structural Rheology of a Model Cream", Journal of the Society of Cosmetic Chemists, **45**, 77-84, 1994.

LE Pena, BL Lee and JF Stearns, "Videomicroscopy Techniques for Agglomeration Studies", Pharmaceutical Research, **11**, 600-603, 1994.

LE Pena, BL Lee and JF Stearns, "Consistency Development and Destabilization of a Model Cream", Proceedings of the 16th IFSCC Congress, October 1990, New York. Also, Journal of the Society of Cosmetic Chemists, **44**, 337-345, 1993.

LE Pena, "Gel Dosage Forms-Theory, Formulation and Processing", in Topical Drug Delivery Formulations, DW Osborne and AH Amann, ed., Marcel Dekker, Inc., New York, New York, 1990.

LE Pena and BJ Sandmann, "Gel Development in Surfactant Systems", Second International Conference on Pharmaceutical Technology, Association de Pharmacie Galenique Industrielle, Paris, France, 1980.

LE Pena, "Rheology and Solution Structure of Gum-Surfactant and Micelle Systems", Doctoral Dissertation, University of Missouri-Kansas City, School of Pharmacy, Kansas City, Missouri, 1980.

Presentations:

Seminar Presentations:

LE Pena, BL Lee and JF Stearns, "The Impact of Shampoo Minor Components on the Degradation of Methylchloroisothiazolinone and Methylisothiazolinone", Annual Scientific Seminar, Society of Cosmetic Chemists, Las Vegas, Nevada, May 1994.

LE Pena, BL Lee and JF Stearns, "Consistency Development and Destabilization of a Model Cream", 16th IFSCC Congress, New York, October 1990.

LE Pena, "Gel Dosage Forms-Structure and Formulation", 61st Colloid and Surface Science Symposium, American Chemical Society, Ann Arbor, Michigan, June 1987.

LE Pena, "Rheology Case Studies of Topical Products", Midwest Regional Meeting, AAPS, Chicago, Illinois, May 1987.

LE Pena, "Sometimes It's the Little Things That Count", Symposium on Product Development Problems and Their Resolutions, AAPS National Meeting, Washington D.C., November 1986.

LE Pena and BJ Sandmann, "Liquid Crystalline Surfactant Systems.II. Rheology", Basic Pharmaceutics, Academy of Pharmaceutical Sciences Annual Meeting, San Antonio, Texas, November 1980.

BJ Sandmann, LE Pena and R Coveney, "Liquid Crystalline Surfactant Systems. I. Characterization", Basic Pharmaceutics, Academy of Pharmaceutical Sciences, Annual Meeting, San Antonio, Texas, November 1980.

LE Pena and BJ Sandmann, "Gel Development in Surfactant Systems", Second International Conference on Pharmaceutical Technology, Association de Pharmacie Galenique Industrielle, Paris, France 1980.

LE Pena and BJ Sandmann, "Rheological Characterization of Gum-Surfactant Systems", Basic Pharmaceutics, Academy of Pharmaceutical Sciences, Annual Meeting, Kansas City, Missouri, November 1979.

Poster Presentations:

LE Pena, GE Padbury, and BD Rush, "Rat Bioavailability Studies of the Chroman Amine Antioxidant U-83836E in Suspension and Solution", AAPS Annual Meeting, Indianapolis, Indiana, November 2000.

LE Pena, "*In Vitro* Drug Release Studies for Topical Products: An Overview of Parameters", Advances in the Biology and Treatment of the Skin, Environmental and Occupational Health Sciences Institute, Piscataway, New Jersey, June 1999.

LE Pena, "*In Vitro* Drug Release Studies for Topical Products: Experimental Studies", Advances in the Biology and Treatment of the Skin, Environmental and Occupational Health Sciences Institute, Piscataway, New Jersey, June 1999.

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DA Hatzenbuhler, JE Browne, DJ Whitaker, AE Zieve, KD Baker and LE Pena, "Rogaine Formulation Alternatives", Topical Drug Products Workshop, Arlington, Va., March 1990.

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